PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	27.05.2010
Applicant's or agent's file reference 44654	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2008/001678	25.12.2008	26.12.2007

Applicant
SENG ENTERPRISES LIMITED

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 44654	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IL2008/001678	International filing date *(day/month/year)* 25.12.2008	Priority date *(day/month/year)* 26.12.2007
International Patent Classification (IPC) or national classification and IPC INV. B01L3/00		
Applicant SENG ENTERPRISES LIMITED		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see paragraph 3*bis* of Annex C of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2009-12-10	27.05.2010
Name and mailing address of the international preliminary examining authority: European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Authorized officer Viskanic, Martino Telephone No. +31 70 340-9899

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IL2008/001678

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-33 as originally filed

Claims, Numbers

1-64 filed with the demand for preliminary international examination

Drawings, Sheets

1/28-28/28 as originally filed

☐ a sequence listing - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-13, 15, 21-33, 39-59

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*.

☒ no international search report has been established for the said claims Nos. 11-13, 15, 21-33, 39-59

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-4, 7, 8, 10, 17, 18, 20, 34-38, 63, 64
	No:	Claims	1, 5, 6, 9, 14, 16, 19, 60-62
Inventive step (IS)	Yes:	Claims	2-4, 34-38, 63
	No:	Claims	1, 5-10, 14, 16-20, 60-62, 64
Industrial applicability (IA)	Yes:	Claims	1-10, 14, 16-20, 34-38, 60-64
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1 Claims 11-13, 15, 21-33, 39-59 have not been examined, as they were not considered in the search report (Rule 70.2(d) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

2 The subject matter of amended claim 1 is considered not to be novel (Art. 33 (1)(2) PCT) over D3. In detail:
D3 discloses: A cell study device (cf. [0064], where the antibody production of cells trapped in the device can be studied), comprising: a base layer (cf, fig. 1a (13);
a planar conduit defining layer (12), separate from said baselayer, including a channel (15) open at the top and bottom therein;
a planar cover layer (11), separate from said base (13) and conduitdefining (12)layers, which, together with the walls of said channel and said base layerforms an enclosed capillary flow channel (cf. title: "microfluidic") in said conduit layer; and a cell holding area on said base layer in fluid contact withsaid capillary flow channel, said cell holding area being sized and configured toaccommodate and immobilize a single cell or a number of cells for exposure to a sequence of liquidaliquots, thereby permitting study of cells individually, said layers being formed of materials that do not interferewith cell behavior over a period of at least 5 hours when loaded with aqueoussolution.
In D3, [0064], it is stated that "coating materials can be applied to the microfluidic system prior to use that ... promote ... cellular binding to surfaces. In this manner cells can be localised (i.e. held) within the microfluidic device where desired in order to perform cellular synthesis such as antibody production".
The qualitative or quantitative monitoring of the antibody production of selected cells is considered to be a cell study, and the channels coated with materials promoting the immobilisation of cells within the channels lead to "cell holding areas", whereby the cells can be exposed to a sequence of liquids.
The inertness of the materials used in D3 is stated in [0055].

2.1 The subject matter of the following dependent claims is not novel (Art. 33(1)(2) PCT) over D3 either:
Claim 5: cf. fig. 15B.
Claims 6, 9: cf. fig. 1 (14).
Claim 14: cf. fig. 1B.
Claim 16: cf. [0034].
Claim 19: cf. [0055].
Claim 60: cf. [0045].
Claim 61: cf. [0041].
Claim 62: cf. fig. 1B.

2.2 The subject matter of dependent claims 7, 8, 10, 17, 18, 20, 64 relates to constructional modifications of the device in D3 that the skilled person would implement in order to optimise the device without exerting inventive skills (Art. 33(3) PCT).

2.3 The remaining dependent claims 2-4, 34-38, 63 are novel (Art. 33(1)(2) PCT) over D3 and appear to be inventive (Art. 33(3) PCT).

Re Item VIII

Certain observations on the international application

3 In claim 1 the wording: "said cell holding area...number of cells" is too vague, as the single call has a size which can somehow be figured out by the skilled person, while a "number of cells" can refer to any organism and is therefore not limiting. Thus claim 1 does not comply with Art. 6 PCT.

3.1 Furthermore in the description reference is made to "picowells" (cf. page 7, line 25 - page 8, line 38) which are capable of trapping cells. Since there are also other methods for trapping cells, such as driving the liquid over a surface covered with cell-specific antibodies, but only the mechanical trapping exposed in connection with picowells is disclosed in the description, this feature is considered to be essential and should be present in claim 1.

3.2 Furthermore the wording "thereby permitting..." represents a result to be achieved, as to obtain this result it is necessary that at least the cover is transparent or openable. But these features are considered optional, as they are stated in dependent claims. If the light of the above mentioned wording, at least one of the two features of the cover is considered essential and should thus have been included in claim 1.

3.3 Claim 1 in its last part ("wherein .... solution.") tries to define the claimed subject matter by relation to the use of the device. This results in a lack of clarity (Art. 6 and Rule 6.3(a) PCT), as the technical features required are not unambiguously identifiable, being these subject to modifications according to the conditions of use (e.g. the temperature). It would have been more appropriate to define the materials like in the description, on page 16, lines 17 - 19 as "biologically inert". Similar argumentation applies also to claim 19, which is deemed to be unclear in the meaning of Art. 6 PCT.

3.4 Claim 19 is unclear (Art. 6 PCT), as it is not specified if the materials claimed should not interfere between them or with the sample. In that case it still represents a result to be achieved, as the features which lead to such a behaviour are not self-evident.

3.5 In claim 63 reference is made to all the preceding claims that have been searched. The "array", as claimed in claim 63, finds its precedent in claim 34 and not in claim 1-10, 14, 16-20. Thus claim 63 should refer only to claims 34-38 and 60-62.

CLAIMS

1. A cell study device, comprising:

a base layer;

a planar conduit defining layer, separate from said base layer, including a channel open at the top and bottom therein;

a planar cover layer, separate from said base and conduit defining layers, which, together with the walls of said channel and said base layer, forms an enclosed capillary flow channel in said conduit layer; and

a cell holding area on said base layer in fluid contact with said capillary flow channel, said cell holding area being sized and configured to accommodate and immobilize a single cell or a number of cells for exposure to a sequence of liquid aliquots, thereby permitting study of cells individually,

said layers being formed of materials that do not interfere with cell behavior over a period of at least 5 hours when loaded with aqueous solution.

2. A device according to claim 1, wherein said cell holding area is formed by a well in said base layer.

3. A device according to claim 2, wherein said cell holding area includes at least one orientation mark visible under microscopy.

4. A device according to claim 2 or claim 3, wherein said cell holding area is masked by a masking layer underlying said conduit layer.

5. A device according to any of claims 1-4 including a plurality of cell holding areas in fluid communication with said capillary flow channel.

6. A device according to any of claims 1-5, wherein said cover layer includes one or more air holes in communication with the respective cell holding areas for air release from said cell holding areas.

7. A device according to any of claims 1-6, wherein said capillary flow channel terminates at a distal end thereof in a substantially sealed waste reservoir with no fluid exit.

8. A device according to any of claims 1-6, wherein said capillary flow channel terminates at a distal end thereof in a substantially sealed waste reservoir with an absorbent material as a fluid exit.

9. A device according to any of claims 1-8, further including a fluid inlet area for said capillary flow conduit formed in said cover.

10. A device according to any of claims 1-9, packaged in vacuum.

11. A device according to any of claims 1-10, wherein said conduit layer is permanently adhesive to said cover layer.

12. A device according to claim 11, wherein said device is provided with a removable non-stick layer intermediate most of said cover layer and said conduit layer.

13. A device according to any of claims 1-10, wherein said conduit layer is temporarily adhesive to said cover layer.

14. A device according to any of claims 1-13, wherein said device is formed essentially of layered planar layers.

15. A device according to any of claims 1-14, wherein said conduit layer is adhesive on both its faces.

16. A device according to any of claims 1-15, wherein said layers are selected of dissimilar materials with dissimilar contact angles with fluids.

17. A device according to any of claims 1-16, wherein said device has the form factor of a standard microscope slide.

18. A device according to any of claims 1-16, wherein said device has the form factor of a standard microtitter plate.

19. A device according to any of claims 1-18, wherein said materials do not interfere for at least 24 hours.

20. A device according to any of claims 1-19, wherein said cover layer is openable for access to each of said cell holidng areas and removal of cells therefrom.

21. A kit, comprising:

(a) a cell study device including a capillary flow conduit and a cell holding area; and

(b) at least an indication of one or both of a capillary flow rate and a cell dislocation rate therein.

22. A kit according to claim 21, comprising a plurality of different cell study devices, each with different sets of flow rate and dislocation rate.

23. A kit according to claim 21 or claim 22, wherein said indication is per one or both of fluid property and cell type.

24. A kit according to any of claims 21-23, wherein said indication comprises a machine input indication.

25. A kit according to any of claims 21-24, wherein said indication comprises a human readable indication.

26. A kit according to any of claims 21-25, including instructions explaining said indications.

27. A kit according to any of claims 21-26, including software on a computer readable media for using said indications.

28. A pre-assembled and packaged cell study device including:

a capillary flow conduit;

a cell holding area; and

at least one non-adhesive layer, designed for removal and interfering with adhesion of at least two parts of said device, said interfering inactivating said capillary flow conduit .

29. A device according to claim 28, wherein said adhesion is permanent, when said non-adhesive interfering layer is removed.

30. A method of assembling a cell study device, comprising:

(a) selecting desired device characteristics;

(b) selecting device components from a set of pre-manufactured components, said selected components selected to interact to provide said characteristics; and

(c) assembling said components to provide said device with said desired characteristics.

31. A method according to claim 30, wherein said set includes components of difference wettability.

32. A method according to claim 30 or claim 31, wherein said set includes components defining different capillary flow conduit geometries.

33. A method according to any of claims 30-32, wherein said set includes components defining different cell holding area geometries.

34. A cell study device according to any of claims 1-10, 14 and 16-20 comprising:
at least one array of cell holders; and
a double sided adhesive layer masking some of said cell holders,
wherein said conduit defining layer is mounted on said adhesive layer.

35. A device according to claim 34, wherein said device comprises a plurality of fluidicly disconnected cell holder arrays.

36. A device according to claim 35 wherein each array includes one or more capillary flow channels separate from capillary flwo channels associated with the other arrays.

37. A device according to any of claims 34-36 wherein said adhesive layer is apertured.

38. A device according to any of claims 34-37, wherein said walls are at least 2 mm high.

39. A method of forming a cell study device, comprising adhering a plurality of precut dry or wet layers by applying pressure and defining at least one capillary flow channel between layers, thereby.

40. A method according to claim 39, comprising:
annealing said device under heat;
soaking said device in a solvent matched to said adhering; and
washing away said solvent.

41. A method according to claim 39 or claim 40, comprising embossing a cell holding area on said device.

42. A method according to claim 39, comprising essentially of said adhering.

43. A method according to any of claims 39-42, wherein said adhering comprises adhering, or post treatment, in a low atmospheric pressure condition.

44. A method of studying cells, comprising:

(i) determining one or both of desired flow rates for fluid used during a study and a rate of cell dislocations for a cell type or aggregate used during the study;

(ii) selecting a cell study device including a capillary flow conduit and a cell holding area to match said determinations; and

(iii) using said selected device with said cell type in said study.

45. A method according to claim 44, wherein selecting comprises selecting from a plurality of devices in a kit.

46. A method according to any of claims 44-45, wherein selecting comprises selecting according to a catalog.

47. A method according to any of claims 44-46, wherein selecting comprises recommending by a computer.

48. A method according to any of claims 44-47, wherein selecting comprises a device according to a contact angle between fluid used in the study and said capillary flow conduit.

49. A method according to any of claims 44-48, wherein selecting comprises a device according to a conduit cross-section.

50. A method according to any of claims 44-49, wherein said device has a capillary flow rate of less than 1 micro-liter per second.

51. A method according to any of claims 44-50, wherein said device has a cell dislocation rate of less than 10% per said study.

52. A method according to any of claims 44-51, wherein said device includes at least one baffle to control capillary flow rate.

53. A method according to any of claims 44-52, wherein said device includes a substantially sealed exit reservoir with at least one air hole to control capillary flow rate.

54. A method according to any of claims 44-53, wherein said device includes side walls in said capillary flow conduit which control capillary flow rate.

55. A method according to any of claims 44-54, wherein said device includes one or more changes in geometry at said cell holding area, which changes control cell dislocation rate.

56. A method according to any of claims 44-55, wherein said device allows application of cells directly to said cell holding area without capillary flow.

57. A method according to any of claims 44-56, wherein said selecting comprises selecting according to a desired delivery rate of cells along said capillary flow to said cell holding area.

58. A method according to any of claims 44-57, wherein said cell holding area comprises non-adhesive picowells.

59. A method according to any of claims 44-58, comprising modifying a fluid used during a study to maintain said desired rate.

60. A cell study device according to any of claims 1-10, 14, 16-20, and 34-38, wherein said cover layer is transparent.

61. A cell study device according to any of claims 1-10, 14, 16-20, 34-38, and 60, wherein said cover layer is flexible.

62. A cell study device according to any of claims 1-10, 14, 16-20, 34-38, and 60-61, wherein said cover layer ispartially adherent to said conduit layer.

63. A cell study device according to any of claims 1-10, 14, 16-20, 34-38, and 60-62, wherein said array is defined by a plurality of closely packed pits in the surface of said base layer.

64. A cell study device according to any of claims 1-10, 14, 16-20, 34-38, and 60-63, wherein said channel walls are at least 2 mm high.